EFFECTS OF FOOD ON ETHANOL METABOLISM

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SUMMARY

The goals of the present study were (1) to obtain ethanol pharmacokinetic data from fed dogs, and (2) perform Monte Carlo simulation to determine the effect of food on pharmacokinetic model parameter values. To a cohort of five fed dogs, 1 g ethanol per km body weight was administered as a gavage of 20% w/v ethanol solution. Blood samples taken at 0, 10, 20, 30, 40, 60, 80, 100, 120, 180, 240, and 360 minutes after the dose were mixed with anti-coagulant and stored on ice. Blood ethanol concentration was determined via headspace chromatograph. Monte Carlo simulation with an ethanol pharmacokinetic model was used to estimate model parameter values and parameter standard deviations by minimization of the chi-squared function. Results indicate that 50.6 ± 21.0% of the ethanol dose was absorbed in the stomach, and an insignificant amount of ethanol was metabolized by gastric alcohol dehydrogenase postulated for the model. At 6 hours after the ethanol dose 59.4 ± 21.0% of the ethanol dose was retained in the dogs' stomachs.

KEY WORDS

ethanol, pharmacokinetics, food, Monte Carlo, dog

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INTRODUCTION

Numerous researchers have investigated the effects of food on ethanol metabolism. Reports have demonstrated interaction between food and ethanol metabolism manifest by reduced blood ethanol concentration, delayed peak blood ethanol concentration, reduced area under the blood ethanol concentration curve (AUC), or an increased rate of ethanol elimination from blood. Studies compared fasted subjects with subjects fed prior to an oral ethanol dose, while other studies compared fasted subjects with subjects fed after an oral dose of ethanol. Others studied the effects of a meal on intravenously (i.v.) administered ethanol. The effect of food on ethanol has been variously attributed to food's delay of gastric emptying or food's acceleration of ethanol metabolism, among other possible effects.

Mellanby /1/ demonstrated that food was associated with reduced blood ethanol concentrations. Widmark /2,3/ reported that amino acids reduced blood ethanol concentrations by greater amounts than fatty acids.

Southgate /4/ found that a water meal followed by oral ethanol did not significantly affect blood alcohol concentrations relative to fasted control subjects, but that a meal of whole milk and bread followed by oral ethanol reduced blood alcohol concentration by 21.4% ($p < 0.008$) below that of fasted controls. Eggleton /5/ demonstrated in cats that i.v. infusion of alanine (2-6 g) increased the linear rate of ethanol metabolism by 34.7% relative to controls ($p = 0.014$) and that the effect was dose dependent ($R^2 = 0.906$) in the range of alanine evaluated. In human subjects, Miller and Stirling /6/ observed an increase in the mean maximum rate of ethanol elimination following consumption of a meal. In an effort to determine the site of post-prandial gastrointestinal ethanol absorption, Cortot *et al.* /7/ determined that 73.2% of ethanol was absorbed in the stomach with 24.0% absorbed in the duodenum. Cooke and Birchall /8/ determined that 28.7% of ethanol in a glucose solution (100 g/l) was absorbed from the stomach in 30 minutes. In a study with 14 human subjects, Sedman *et al.* /9/ determined that the AUC was significantly lower when ethanol was administered with a liquid meal than without a meal; they also found that protein-, carbohydrate-, and fat-containing meals significantly depressed the peak blood ethanol concentration and delayed the time of occurrence of the peak. In a study using meals

of solid food, Lin *et al.* /10/ determined that each of the meals reduced the AUC relative to the fasting state; meals administered prior to the oral ethanol dose reduced peak blood ethanol concentration. McFarlane *et al.* /11/ demonstrated that a dietary lipid emulsion administered directly to the ileum or the duodenum significantly delayed gastric emptying and reduced blood ethanol concentration values in a cohort of six human subjects. Rogers *et al.* /12/ evaluated the effects of protein, carbohydrate, and fat meals on metabolism of i.v. infused ethanol and found that the carbohydrate meal increased the ethanol elimination rate by 60% over that of a fasting state.

In a study in rats, Tachiyashiki and Imaizumi /13/ observed that an oral dose of soybean oil, coconut oil, linoleic acid, oleic acid, or linolenic acid, delivered 30 minutes prior to an oral ethanol dose, reduced blood ethanol concentration values and the AUC significantly below those of fasted controls. The oils and fatty acids also delayed the appearance of the peak blood ethanol concentration. The effects of the oils and linoleic acid on blood ethanol response resulted from delayed gastric emptying.

Jones and Jönsson /14/ studied the effect of food on ethanol absorption and on the rate of blood ethanol elimination in a cohort of ten humans. Subjects who consumed a meal 30 minutes prior to an oral ethanol dose had significantly lower blood ethanol concentrations than subjects who had fasted prior to the same oral ethanol dose. The AUC of the fed subjects was also reduced significantly relative to the fasted subjects. In the same study, fasted subjects who consumed a meal 5 hours after an oral ethanol dose experienced 50% increased rate of ethanol elimination from blood relative to fasted subjects who did not consume a meal.

Using 12 human subjects, Hahn *et al.* /15/ evaluated the effect of food on i.v. administered ethanol. Five of 12 fasted subjects consumed a breakfast meal and all subjects were then i.v. infused with ethanol (0.4 g/kg). Later the same day, after ethanol was no longer detectable in any subject, the seven fasted subjects consumed a lunch meal while those who had earlier consumed breakfast continued to fast. All subjects were then i.v. infused again with ethanol (0.4 g/kg). In each of the two feeding epochs the ethanol elimination rate in the fed subjects was 60% greater than ethanol elimination in the non-fed subjects.

A study using nine human subjects compared the effects of a high-fat, high-carbohydrate, or high-protein meal with fasted subjects when challenged by a postprandial oral ethanol dose (0.3 g/kg) or i.v. ethanol dose (0.3 g/kg). Each of the three types of meals significantly depressed the peak blood ethanol concentration and the AUC below that of the fasted state or i.v. infusion; there were no significant differences in blood ethanol response between the three types of meals /16/.

It appears clear that ethanol absorption from the gastrointestinal tract, meal and meal composition, gastric emptying, and ethanol elimination are interrelated /17/. Although two reports of ethanol pharmacokinetic models explicitly included equations for gastric emptying, those reports did not evaluate model parameter significance using Monte Carlo simulation /18,19/.

The overall objective of the present study was to evaluate ethanol pharmacokinetics in fed dogs. Specific aims were: (1) to measure blood ethanol concentrations from a cohort of five fed dogs challenged with a single bolus oral dose of ethanol; (2) to use Monte Carlo simulation with an ethanol pharmacokinetic model and the measured blood ethanol concentrations to obtain values for seven model parameters for the fed dogs.

MATERIALS AND METHODS

Ethanol pharmacokinetic model

Earlier we reported an ethanol pharmacokinetic model which accounted for the following processes /20/:

1. The distribution volume for ethanol is the total body water.
2. The distribution volume for ethanol is well mixed; therefore, the blood and the extravascular space excluding the stomach and small intestine are essentially equilibrated.
3. The stomach is a separate compartment.
4. Gastric alcohol dehydrogenase is present in the stomach mucosa which oxidizes ethanol according to a Michaelis-Menten rate-expression.

5. The small intestine includes the duodenum and is a separate compartment.
6. Ethanol elimination from the total body water can be described as a Michaelis-Menten rate-expression at the ethanol concentration of interest.
7. Ethanol transport occurs in either direction by passive diffusion through the stomach wall.
8. Ethanol transport occurs in either direction by passive diffusion through villi of the small intestine.
9. Ethanol can flow from the stomach to the duodenum through the pyloris.

Total body water and hepatic alcohol dehydrogenase (LADH)

Ethanol is transported via normal circulation out of the total body water compartment to the small intestine and stomach compartments where diffusion can occur in either direction into or out of the stomach and small intestine. Ethanol returns to the total body water compartment from the small intestine and stomach compartments via normal circulation. V_{max} and K_m for LADH were two of the variables determined by fitting experimental data to the proposed model.

Stomach

The diffusion model for the stomach consists of normal circulation containing ethanol flowing into a well-mixed vascularized mucosa. Ethanol diffuses across an epithelial layer between the well-mixed mucosa and the stomach lumen. The model parameter characterizing ethanol diffusion in the stomach mucosa is $ks \cdot Am$ which is the product of the mass transfer coefficient for ethanol, ks (cm/min) and the area available for ethanol transport, Am (cm^2).

Small intestine

The diffusion model for the small intestine consists of normal circulation containing ethanol flowing through the villi into a well-mixed compartment adjacent to the small intestine. Ethanol diffuses across an epithelial layer between the well-mixed compartment and the small intestine lumen. The model parameter characterizing ethanol

diffusion in the small intestine is $kd \cdot Al$ which is the product of the mass transfer coefficient for ethanol, *kd* (cm/min) and the area available for ethanol transport, *Al* (cm^2).

Gastric alcohol dehydrogenase (GADH)

GADH can be found throughout the gastrointestinal tract of humans. Presumably this ADH is responsible in part for the first-pass metabolism of ethanol documented by Risto *et al.* /21/ and others, where as much as 20% of an oral dose of ethanol did not appear in the vascular space. However, the magnitude of gastric first-pass metabolism of ethanol has been challenged by Derr /22/ and others. This argument notwithstanding, we assumed for the present model that GADH exists in the stomach mucosa of dogs. V_{max} and K_m for this putative GADH were two of the variables determined by fitting our experimental data to the proposed model.

Gastric emptying

The rate of gastric emptying into the small intestine is proportional to the difference between the volume of the stomach lumen contents and the resting stomach volume. Alpha (α) (min^{-1}) is the proportionality constant that characterizes gastric emptying.

Ethanol dosing and blood ethanol determination

Each dog in a cohort of five dogs remained on a normal feeding schedule and was fed one can (418 g) of Hill's Science Diet Canine Adult (6.0% protein, 3.9% fat, 13.0% carbohydrate) 30 minutes prior to the ethanol dose. The same cohort was used in an earlier study to study ethanol metabolism in the fasted state /20/; results from the earlier study are compared with data from the present work.

Each dog was shaved and swabbed with Betadine solution at the venipuncture site prior to blood sampling. Blood (3 ml) was taken from a catheter placed in the saphenous vein for the duration (6 hours) of the experiment. A single blood sample (3 ml) was taken from each dog before the ethanol dose (0 minutes). Additional blood samples were taken at 10, 20, 30, 40, 60, 80, 100, 120, 180, 240, 300, and 360 minutes after ethanol dosing. Blood was mixed with 7.5 mg solid sodium fluoride and 6.0 mg potassium oxalate to prevent coagulation.

Samples and reagents were maintained on ice unless otherwise noted. Standards (1.0 ml) were prepared by mixing 0.9 ml of anticoagulated, ethanol-free blood with ethanol (Aaper Alcohol Co., Shelbyville, KY) solution yielding standard solutions of 0, 2, 4, 6, 12.5, 25, or 60 mM ethanol. Each standard or sample (1 ml) was then mixed with 0.5 ml of perchloric acid (1 N PCA, 20 mM thiourea) (PCA) and centrifuged. Supernatant of 0.6 ml was sealed in glass vials for head-space analysis using a Hewlett-Packard 5890 II gas chromatograph (GC) utilizing a flame ionization detector (FID) with a 183 x 0.6 cm column packed with Tenax GC along with a Hewlett-Packard 19395 autosampler. Samples were incubated in sealed GC vials at 60°C for 10 minutes prior to GC headspace sampling and during GC headspace sampling. Additional ethanol analysis details are given by Whitmire *et al.* /23/.

Chi-squared minimization and Monte Carlo parameter estimation

Chi-squared minimization was used to fit the blood ethanol concentration data to the ethanol pharmacokinetic model. Chi-squared fitting, a version of the common 'least-squares' technique, is based on the chi-squared function shown in equation 1:

$$\chi^2 \equiv \sum_{i=1}^{N} \left(\frac{y_i - y(x_i; a_1 \ldots, a_M)}{\sigma_i} \right)^2 \qquad [1]$$

where, in general, N = number of experimental data points[1], y_i = experimental value of the dependent variable, $y(x_i;a_1...,a_M)$ = computed model value of the dependent variable, x_i = independent variable, $a_1...,a_M$ = model parameters to be determined by fitting[2], and σ_i = standard deviation of the replicated experimental data points at each value of the independent variable. In the present study, the dependent variable was the mean blood ethanol concentration for the five dog cohort, σ_i was the standard deviation of the blood ethanol concentration measurements for the five dog cohort at any of the 14 blood sampling times listed above, the independent variable, x_i, was time after ethanol dosing, and N =14, the number of blood alcohol concentration values for each dog in the cohort. Model parameters ($a_1...,a_M$), the ultimate values of which were determined by fitting,

[1] The number of data points in the present case is 14.
[2] The number of model parameters in the present case is seven.

included α, $kd \cdot Al$, $ks \cdot Am$, $LADH\ V_{max}$, $LADH\ K_m$, $GADH\ V_{max}$, and $GADH\ K_m$. Model parameters were defined earlier.

Chi-squared values were based on the difference between the model value of the blood ethanol concentration and the experimental mean blood ethanol concentration at each of the 14 blood sampling times listed earlier.

The simplex algorithm of Nelder and Mead /24/ and the golden-section search algorithm /25/ were used to adjust each model parameter to minimize χ^2. One thousand simulations were used to obtain the distribution of values for each model parameter.

Monte Carlo simulation of ethanol pharmacokinetics

With the mean and standard deviation established for each model parameter, Monte Carlo simulation was again used, this time to simulate ethanol pharmacokinetics. The pharmacokinetic model was solved 1,000 times using the Runge-Kutta algorithm. For each of the 1,000 solutions, model parameter values were obtained by randomly sampling each parameter distribution. Note that by randomly sampling parameter value distributions, combinations of the seven model parameters not likely to occur in nature may be included for Monte Carlo simulation; however, since unrealistic combinations of parameter values, if they occur at all, are far less probable than realistic combinations of parameter values we obtain useful results centered about a mean blood ethanol concentration at each time value from Monte Carlo simulation.

The structure of the model allows for individual consideration of stomach and intestinal ethanol absorption and gastric and hepatic ethanol metabolism. To estimate the ethanol oxidized by either gastric or liver ADH, the Michaelis-Menten rate equation for each was integrated during simulation. Similarly, to estimate ethanol transport in the stomach and intestine, the mass flux equations were integrated during simulation.

RESULTS AND DISCUSSION

Experimental ethanol pharmacokinetics

Mean values of experimental blood ethanol concentration versus time are shown in Figure 1. The peak mean blood ethanol concentration for the fed dogs was 8.61 ± 1.24 mM at 80 minutes after the ethanol dose.

Parameter values from Monte Carlo simulation

Mean values ± standard deviation of the seven adjustable model parameters are given in Table 1. The value of the gastric emptying coefficient (α) was 0.000 min^{-1} indicating quite strongly that food prevented gastric emptying of the ethanol dose; the same parameter from the dogs fasted in the previous study /20/ was 0.031 min^{-1}.

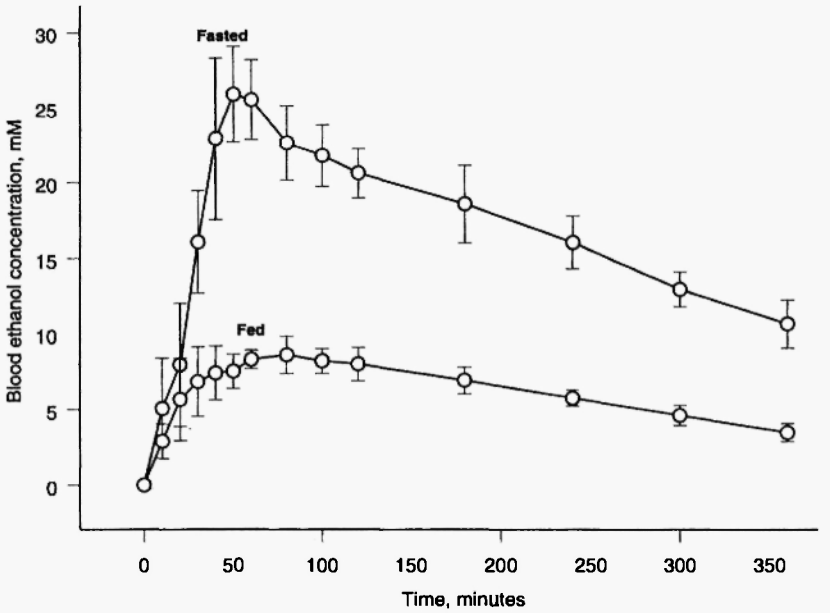

Fig. 1: Blood ethanol pharmacokinetics of fed and fasted dogs (n = 5). Open circles indicate the mean of the experimental blood ethanol concentration (mM) values. Bars indicate ± 1 standard deviation. Fasted dog data are from /20/.

TABLE 1

Adjustable parameters from Monte Carlo simulation

Model parameter	**Fasted dogs** (n = 5)	**Fed dogs** (n = 5)
GADH V_{max} (mmole ethanol/min-l mucosa)	15.44 ± 29.63	47.36 ± 46.64
GADH K_m (mM)	1331.5 ± 866.67	1283.2 ± 597.52
LADH V_{max} (mmole ethanol/min-l body water)	0.612 ± 0.034	0.767 ± 0.045
LADH Km (mM)	102.97 + 7.55	102.159 ± 5.78
Gastric mass transport factor (ks·Am, cm^3/min)	0.643 ± 0.273	0.559 ± 0.265
Intestinal mass transport factor (kd·Al, cm^3/min)	4.363 ± 1.349	0.313 ± 0.697
Gastric emptying factor (alpha, min^{-1})	0.031 + 0.001	0.000 ± 0.000

Results are means ± SD.
ks·Am is the product of the mass transfer coefficient (km, cm/min) and the gastric area for ethanol transport (cm^2).
kd·Al is the product of the mass transfer coefficient (kd, cm/min) and the intestinal area for ethanol transport (cm^2).

The GADH V_{max} for fed dogs was three-fold greater than for the same cohort of dogs fasted in the previous study /20/, indicating that food may have potentiated the specific activity of GADH. GADH K_m was unaffected by the feeding status of the dogs. In addition, standard deviations for both GADH V_{max} and GADH K_m parameters were approximately the same magnitude as the mean values of the parameters, which may tend to indicate that the actual values of these parameters have little impact on ethanol metabolism in the subjects tested.

The liver ADH K_m values determined by simulation were not affected by the dogs' feeding status. The liver V_{max} was 0.767 ± 0.045

mmole ethanol/min-l body water for fed dogs, 25.3% greater than the V_{max} when the dogs were fasted (0.612 ± 0.034 mmole ethanol/min-l body water) /20/. This increase in hepatic ADH, apparently an effect of the meal, seems to indicate that food potentiated liver ADH activity similar to what was observed in several previous studies.

Monte Carlo simulation of ethanol pharmacokinetics

The structure of the model allowed for individual consideration of the metabolic fate of the ethanol dose. The model predicted that 23.8 ± 8.3% of the ethanol dose was absorbed by the stomach in fasted dogs /20/ which is similar to the value of 10% reported by Levitt *et al.* /26/. In fed dogs the predicted value of ethanol absorption in the stomach was 50.6 ± 21.0%. In fasted dogs, the model predicted 82.8 ± 8.1% of the ethanol dose was absorbed in the intestine /20/; since gastric emptying was completely eliminated by the meal, the model predicted that no ethanol was absorbed by the intestine in fed dogs. The model also predicted that 2.55 ± 5.35% of ethanol oxidation was catalyzed by gastric alcohol dehydrogenase in fasted dogs /20/ and 2.15 ± 3.39% in fed dogs. Gastric ethanol oxidation was characterized by considerable variance but the mean value was similar to the value of 0.24% predicted by Derr /27/ and the negligible gastric metabolism predicted by Levitt *et al.* /26,28/.

In the case of the fed dogs the model predicted that only 50.6 ± 21.0% of the ethanol dose was absorbed by the stomach and no ethanol was absorbed in the intestine. Moreover, from inspection of Figure 1, it is clear that the fasted AUC was significantly greater than the fed AUC for the period from 0 to 360 minutes. The difference in the fasted and fed AUC values can be interpreted as ethanol that did not appear in the vascular space. Therefore, the fate of ethanol not appearing in the vascular space is subject to some explanation.

Beginning in 1985 there have been reports that ethanol not appearing in the vascular space was oxidized by GADH /21/ as gastric first-pass metabolism, while others disagreed with the hypothesis of gastric first-pass metabolism. Our results indicate gastric first-pass metabolism of the ethanol dose of only 2.55 ± 5.35% for fasted dogs /20/ and 2.15 ± 3.39% for fed dogs. The model also indicated that 59.4 ± 21.0% of the ethanol dose was retained in the stomach of fed dogs at 360 minutes, thus accounting for ethanol not appearing in the vascular space. Stomach retention of this ethanol in the fed dogs was

caused by elimination of gastric emptying in the fed dogs and the relatively slow diffusion of ethanol through the stomach mucosa. Stomach retention of ethanol resulted in stomach ethanol concentrations of 250-800 mM for fed dogs compared with 3-5 mM in fasted dogs /20/ at 360 minutes; in both cases the initial gastric ethanol concentration exceeded 3,000 mM. We speculate that retained ethanol in the fed dogs will eventually appear in the vascular space but only at relatively low concentrations; the retained ethanol will slowly diffuse through the stomach mucosa and, as gastric emptying is restored, retained gastric ethanol will empty into the small intestine and be absorbed through the small intestine. However, at 360 minutes the blood ethanol concentration in fed dogs was 3-5 mM, several-fold lower than the fasted dog blood ethanol concentration (10-13 mM) /20/ at the same time. Thus, even though the model predicts that all retained gastric ethanol will appear in the vascular space, the resulting blood ethanol concentrations will remain relatively low. With careful blood ethanol measurements over a sufficiently long period of time we believe that the dogs' fed and fasted AUC values would ultimately become equal.

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